Glucose metabolism in osteoporosis: A potential therapeutic target (Review)

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Abstract. Osteoporosis is a systemic skeletal disease characterized by progressive bone loss and an increased risk of fracture, and it represents a major public health challenge worldwide. Osteoporosis has multiple pathogenic determinants, including age, endocrine disorders and medication. Current therapeutic approaches primarily aim to promote osteogenesis directly or inhibit osteoclast activity; however, these strategies may limit therapeutic efficacy and increase the risk of adverse effects. The present review provided an integrated perspective on the pathogenesis of osteoporosis from the standpoint of glucose metabolism. Glucose oxidation generates ATP and metabolic intermediates that are key to bone homeostasis. During early differentiation, mesenchymal stem cells rely predominantly on glycolysis during commitment toward pre-osteoblasts, whereas maturation into functional osteoblasts depends more notably on oxidative phosphorylation. The fusion and differentiation of osteoclasts require robust mitochondrial oxidation. Lactate derived from anaerobic metabolism has a dual role in bone metabolism. High-risk populations for osteoporosis include postmenopausal women, patients with type 2 diabetes mellitus and individuals with obesity. Estrogen exerts anti-inflammatory and antioxidant effects through receptor activation. Excessive production of advanced glycation end-products disrupts the bone matrix, whereas hyperlipidemia promotes inflammatory factor-induced bone resorption. These pathological changes disrupt the insulin receptor substrate/PI3K/AKT signaling pathway, compromise glucose transporter-mediated cellular glucose uptake and thus, contribute to relative insulin resistance and insufficiency compared with physiological states. In conclusion, the present review demonstrated that abnormal glucose metabolism is a key pathogenic mechanism in osteoporosis and that targeting insulin signaling may represent a fundamental strategy for correcting glucose metabolic abnormalities across diverse etiologies.

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Abbreviations: PPP, pentose phosphate pathway; GLUT, glucose transporter; BMD, bone mineral density; TCA cycle, citric acid cycle; OXPHOS, oxidative phosphorylation; HK, hexokinase; PFK-1, phosphofructokinase-1; PK, pyruvate kinase; PDK, pyruvate dehydrogenase kinase; IDH, isocitrate dehydrogenase; α-KGDH, α-ketoglutarate dehydrogenase; MSCs, mesenchymal stem cells; LDH, lactate dehydrogenase; ROS, reactive oxygen species; G6PD, glucose-6-phosphate dehydrogenase; IGF-1, insulin-like growth factor-1; GS, glycogen synthase; GSK-3, glycogen synthase kinase 3; BAIBA, β-aminoisobutyric acid; OVX, bilaterally ovariectomized; ER, estrogen receptor; AGEs, advanced glycation end-products; IRS, insulin receptor substrate; ILs, interleukins

Key words: osteoporosis, glucose metabolism, postmenopausal women, diabetes, obesity

Contents

1. Introduction

Glucose is the principal source of energy and carbon in sustaining biological activity. Carbohydrate metabolism encompasses the breakdown, transport and synthesis of glucose. The major pathways of glucose catabolism include aerobic oxidation, anaerobic glycolysis and the pentose phosphate pathway (PPP) (1). Glucose oxidation generates ATP for cellular functions, whereas its metabolic intermediates contribute to the synthesis of proteins, lipids and nucleic

acids (2). Cellular glucose uptake is mediated by glucose transporters (GLUTs). GLUTs modulate insulin secretion and are reciprocally regulated by insulin, forming a feedback loop key to systemic glucose homeostasis (3). Glycogenesis is the anabolic conversion of glucose into glycogen polymers for storage, primarily in hepatic and skeletal muscle tissues. Hepatic glycogenolysis maintains blood glucose homeostasis, whereas skeletal muscle glycogen serves as an immediate energy reservoir for contractile activity (4). Glucose metabolism is therefore key to maintaining normal cellular physiology. Dysregulated glucose metabolism has been recognized as a fundamental pathogenic process in several diseases, including chronic kidney disease, coronary heart disease and obesity, and targeted modulation of metabolic pathways represents a potential therapeutic strategy (5-7).

Osteoporosis is a metabolic skeletal disease characterized by reduced bone mineral density (BMD) and deterioration of bone microstructure, and osteoporosis has a global incidence rate of 23.1% in postmenopausal women, 27.67% in type 2 diabetic patients and 45.1% in the obese population (8-11). The progression of osteoporosis involves sustained impairment of bone formation and enhanced bone resorption. In the early phase, osteoporosis is often asymptomatic, with no overt manifestations until fracture occurs. Therapeutic efficacy decreases markedly once clinical complications become apparent, particularly in advanced osteoporosis with established fractures (12). Therefore, targeted therapeutic strategies and proactive preventive measures in high-risk populations are key to reducing the burden of osteoporosis. Dysregulated glucose metabolism has been extensively recognized as a pivotal pathogenic mechanism underlying osteoporosis (13-15). Within bone tissue, glucose metabolism contributes to energy supply, redox balance, insulin sensitivity and inflammatory regulation (16). The present review aims to elucidate the role of glucose metabolism in the pathogenesis of osteoporosis and potentially optimize therapeutic strategies for osteoporosis.

2. Aerobic oxidation in osteogenesis and osteoclastogenesis

Aerobic oxidation refers to the metabolic process by which oxygen is used to completely oxidize glucose into carbon dioxide and water. This process mainly comprises three stages: Glycolysis, pyruvate oxidation and the citric acid cycle (TCA cycle) coupled with oxidative phosphorylation (OXPHOS) (17). Glucose is converted to pyruvate in the cytoplasm. Pyruvate then enters the mitochondria, where it undergoes oxidative decarboxylation to form acetyl-CoA. Acetyl-CoA enters the TCA cycle, which is coupled with OXPHOS to generate ATP. Glycolysis serves as the shared initial pathway for both aerobic and anaerobic glucose metabolism. The three key enzymes regulating this process are hexokinase (HK), phosphofructokinase-1 (PFK-1) and pyruvate kinase (PK) (18). The pyruvate dehydrogenase kinase (PDK) complex regulates the conversion of pyruvate to acetyl-CoA. The TCA cycle is primarily catalyzed by citrate synthase, isocitrate dehydrogenase (IDH) and α-ketoglutarate dehydrogenase (α-KGDH) (19).

Osteoblasts are derived from the differentiation of mesenchymal stem cells (MSCs) in the bone marrow. Glycolysis-based metabolic remodeling has been reported to enhance osteogenesis (20). Glucose-label incorporation studies indicated that glycolytic flux increases during the osteogenic differentiation of MSCs (21-23). Glycolysis upregulates runt-related transcription factor 2 (RUNX2), osterix (also known as Sp7) and osteopontin through bone morphogenetic protein 2 (BMP2) and Wnt/β-catenin signaling (24). Increased glycolysis also supports the osteogenic differentiation of MSCs under pathological microenvironmental conditions such as high glucose, oxidative stress and hypoxic conditions (25). Activation of glycolytic signaling has been reported to rejuvenate senescent osteogenic cells (26). Key glycolytic enzymes serve key roles in osteogenic metabolism. HK expression increases during osteogenic differentiation (27). HK interacts with voltage-dependent anion channel-1 to maintain mitochondrial function and support osteogenesis (28). Furthermore, HK activation may increase receptor activator of NF-κB ligand (RANKL) secretion by osteoblasts and elevate the RANKL/osteoprotegerin (OPG) ratio, thereby favoring osteoclast formation and differentiation (29). PFK-1 mediates aerobic glycolysis in osteoblasts (30). PFK-1 activation regulates AKT/ERK1/2 cascades during the osteogenic differentiation of MSCs (20). PK deficiency is also associated with osteoporosis by regulating pyruvate formation (31). Reduced PKM2 expression inhibits lactate secretion, thereby weakening histone H3 lysine 18 lactylation (H3K18la) and osteogenic differentiation of MSCs (32). During aerobic glycolysis, PDK may silence the sclerostin promoter and activate phosphorylated (p)-SMAD1/5/9 to increase BMP9 expression via Wnt/β-catenin signaling (33,34). Pyruvate contributes to osteoblast differentiation by ameliorating oxidative stress (35). PDK reduces reactive oxygen species (ROS) and malondialdehyde levels, thereby promoting osteoblast differentiation and inhibiting ferroptosis (36).

The TCA cycle serves as the primary source of high-energy electrons, driving the electron transport chain on the inner mitochondrial membrane and supporting OXPHOS, which is key to bone formation. Citric acid accumulation is positively associated with mineralized nodule formation (37). Citrate deposition into mineral hydroxyapatite also enhances bone strength (38). α-ketoglutarate is an endogenous metabolic intermediate involved in osteogenic differentiation and mineralization (39). α-ketoglutarate can markedly activate Wnt/β-catenin and PI3K-AKT pathways to promote osteogenesis (40). Energy substrate dependence changes markedly during osteogenic differentiation. In the early stage of differentiation, OXPHOS drives ATP production, whereas mature osteoblasts rely more notably on glycolysis (41). OXPHOS during aerobic oxidation provides a foundation for MSC differentiation (42) and is key to cortical bone mass (43). Na^+/K^+ ATPase promotes hydroxyapatite formation in the bone matrix by transducing phosphate and ATP generated through OXPHOS (44).

Osteoclastogenesis is associated with notable energy demand (45). Mitochondrial biogenesis and oxidative respiration are key to the resorptive activity of osteoclasts (46). Aerobic glycolysis promotes osteoclast differentiation by activating fragment crystallizable γ receptor I (FcγRI)-, hypoxia-inducible factor-1α (HIF-1α)- and Myc-dependent mechanisms (47,48). Glycolytic intermediates are also involved in the expression levels of tartrate-resistant acid

phosphatase (TRAP), osteoclast-associated receptor (OSCAR) and nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) (49). HK-mediated glycolysis induces osteoclast differentiation and inhibits Piezo-type mechanosensitive ion channel component 1/Wnt signaling, thereby weakening osteoblast mineralization (50). HK demethylation also stabilizes RANK by regulating ubiquitin-specific peptidase 14 deubiquitination activity and thereby promotes osteoclastogenesis (51). PK suppresses osteoclast differentiation by inhibiting the RANKL/cAMP response element-binding protein (CREB)/cFOS/NFATc1 pathway (52), whereas PKM2 interacts with p-STAT3 to promote osteoclast-associated gene expression (53). Regulation of PKM2 can markedly inhibit osteoclast gene expression and the differentiation of bone marrow-derived macrophages (54). PKM2 activation can rescue immunoglobulin gene deficiency required for osteoclast differentiation and promote bone resorption (55).

Loss of the pyruvate carrier also markedly inhibits osteoclast differentiation capacity (56). PDK activity has been reported to be positively associated with the expression levels of osteoclastogenesis-associated genes [such as OSCAR, NFATc1 and cathepsin K (CTSK)] and signaling pathways [such as ERK, p65 and Janus kinase (JAK)/STAT] (57). PDK inhibition effectively prevents aberrant osteoclast activation by interfering with the RANKL-CREB-cFOS-NFATc1 pathway (52). Acetyl-CoA regulates histone acetylation and methylation and is involved in modulating osteoclast differentiation and function. Acetyl-CoA is positively associated with CTSK production through Ras homolog enriched in brain 1/mTOR complex 1 signaling (58). Citrate synthase serves a notable role in osteoclast differentiation by regulating protein succinylation (59). IDH activates the activating transcription factor 4-NFATc1-RANKL signaling axis in osteoblasts to promote osteoclastogenesis (60). IDH is also involved in RANKL-mediated osteoclast differentiation by regulating dimethylation of lysine 9 on histone H3 levels in the CTSK promoter region and platelet-derived growth factor-BB secretion (61). α-ketoglutarate participates in M2-like macrophage differentiation by regulating epigenetic reprogramming, thereby preventing osteoclast-derived bone loss (62). α-ketoglutarate also modulates NFATc1 expression and osteoclast maturation through histone methylation (63) (Fig. 1).

3. Anaerobic oxidation in osteogenesis and osteoclastogenesis

Anaerobic oxidation refers to the glycolysis-based process by which pyruvate is reduced to lactate by lactate dehydrogenase (LDH). Under anaerobic conditions, LDH increases lactate synthesis from glucose metabolism and has a positive role in osteogenic differentiation (64). LDH is also a key enzyme in bone mineralization by increasing the expression levels of Sp7, integrin-binding sialoprotein and bone γ-carboxyglutamate protein (BGLAP) (65). Mechanical loading increases LDH expression and thereby enhances bone strength (66). The effects of LDH on osteoclasts may be bidirectional: LDH-mediated lactate synthesis promotes RANKL-induced osteoclast differentiation (67), whereas LDH-mediated ROS production can inhibit osteoclast differentiation (68). STAT3 transcriptionally regulates LDH activity to modulate mitochondrial redox homeostasis in osteoclasts (45).

The impact of lactate on osteogenesis is variable and may be opposing, depending on its concentration and pathophysiological context. Lactate at low or physiological concentrations is favorable for osteogenesis. Physiological lactate increases the expression levels of Sp7 and collagen I through endogenous activation of Wnt/β-catenin signaling (69). Lactate also promotes osteogenic differentiation through the G protein-coupled receptor (GPR) 81-JAK2/AKT-STAT3 signaling pathway (70). Furthermore, lactate can alleviate oxidative stress by increasing the activities of superoxide dismutase (SOD) and catalase (CAT), thereby enhancing osteogenesis and angiogenesis for vascularized bone formation (71). Lactate metabolism also modulates immune infiltration during the osteogenic effects of MSCs (72). Lactate enhances osteogenic differentiation by promoting M2 polarization and inhibiting M1 polarization of macrophages (73). In addition, lactate is commonly incorporated into biomaterials to promote bone formation (74). Lactate-enriched hydrogel scaffolds promote bone regeneration by synergistically regulating angiogenesis and osteogenesis, making them suitable in repairing bone defects (75). Lactate negatively regulates osteoclastogenesis by inhibiting ROS production (76). Lactate-rich compounds have been reported to markedly inhibit bone resorption by reducing TRAP and CTSK expression (77). The aforementioned hydrogel also notably suppresses osteoclastogenesis, alleviates trabecular bone destruction and improves fracture non-union (78) (Table I).

Lactylation is a key post-translational protein modification involved in the regulation of osteogenic differentiation and osteoclast activity (79). Lactate promotes osteogenic gene expression by increasing H3K18la (30). RUNX2 lactylation enhances protein stability and markedly improves osteoblast differentiation (80). Histone lactylation inhibits osteoclast differentiation by decreasing the expression levels of CCAAT/enhancer-binding protein-β and MAPK phosphatase-1 (81). Histone lactylation also decreases NFATc1 expression and inhibits osteoclast maturation (82). Anaerobic glycolysis generates energy rapidly, which may further support acute osteoclast activities, including rapid polarization and secretion. Osteoclasts pump large numbers of protons (H^+) into the sealed bone resorption compartment through V-type ATPases on the ruffled border, lowering the local pH to dissolve hydroxyapatite in the bone matrix (83).

4. Metabolites and key regulatory enzymes of the PPP in bone metabolism

The PPP is a bypass pathway in which the glycolytic intermediate glucose-6-phosphate is converted to fructose-6-phosphate and glyceraldehyde-3-phosphate through oxidation and group-transfer reactions before re-entering glycolysis. The primary role of PPP lies in generating NADPH and ribose-5-phosphate. Glucose-6-phosphate dehydrogenase (G6PD) is the key enzyme of the PPP and is regulated by the NADPH/$NADP^+$ ratio. The PPP may be a major glucose metabolic pathway in osteolineage cells, supporting cell proliferation and extracellular matrix formation (84). The PPP participates in the regulation of OPG and RANKL to

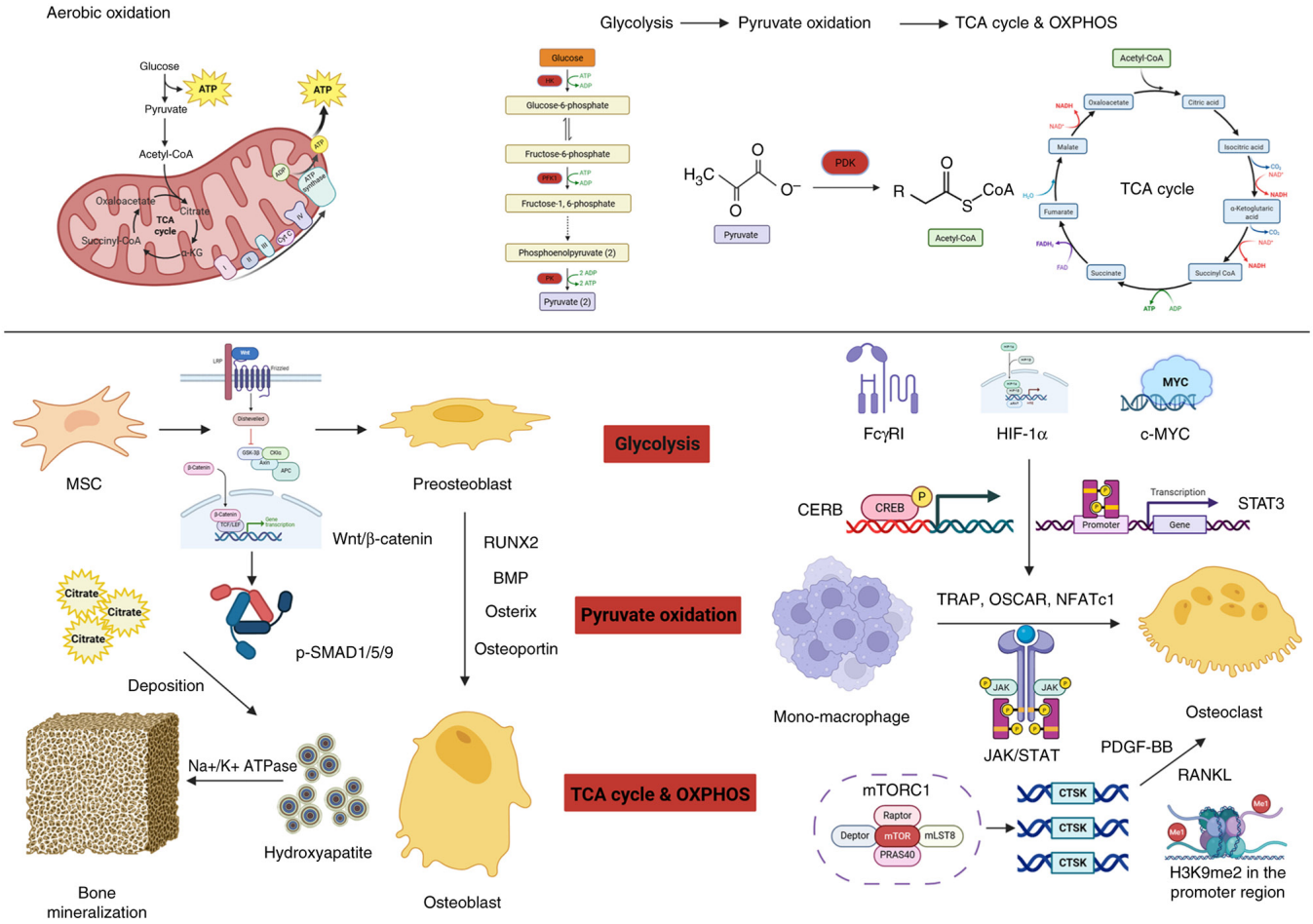

Figure 1. Aerobic oxidation in osteogenesis and osteoclastogenesis. The aerobic oxidation of glucose is divided into three stages: The first stage is glycolysis in the cytosol, which produces pyruvate; the second stage is the oxidative decarboxylation of pyruvate in the mitochondria to form acetyl-CoA; and the third stage includes the TCA cycle and OXPHOS. Glycolysis upregulates RUNX2, osterix and osteopontin through BMP2 and Wnt/β-catenin signaling. Aerobic glycolysis also promotes osteoclast differentiation by activating FcγRI-, HIF-1α- and Myc-dependent mechanisms. The PDK silences the sclerostin promoter and activates p-SMAD1/5/9 to increase BMP9 expression. PDK activity is positively associated with the expression levels of osteoclastogenesis-associated genes (OSCAR, NFATc1 and CTSK) and signaling pathways (ERK, p65 and JAK/STAT). Na^+/K^+ ATPase promotes hydroxyapatite formation in the bone matrix by transducing phosphate and ATP generated through OXPHOS. Black arrows indicate a progressive relationship. Green arrows indicate substance transformation processes. The red line indicates a negative effect. Acetyl-CoA is positively associated with CTSK production through Rheb1/mTORC1 signaling. PDK, pyruvate dehydrogenase kinase; BMP, bone morphogenetic protein; OSCAR, osteoclast-associated receptor; NFATc1, nuclear factor of activated T-cells, cytoplasmic 1; Rheb1, Ras homolog enriched in brain 1; CTSK, cathepsin K; FcγRI, fragment crystallizable γ receptor I; JAK, Janus kinase; mTORC1, mTOR complex 1; RUNX2, runt-related transcription factor 2; OXPHOS, oxidative phosphorylation; p, phosphorylated; HIF-1α, hypoxia-inducible factor-1α; MSC, mesenchymal stem cell; TCA cycle, citric acid cycle.

improve bone metabolism (85). G6PD is closely associated with bone formation and degradation (86). Inhibition of the PPP and G6PD can induce oxidative stress and thereby impair osteogenesis (87,88). Reduced G6PD activity also leads to mitochondrial apoptosis in osteoblasts (89). NADPH, as a reducing hydrogen carrier, promotes osteogenic differentiation and inhibits adipogenic differentiation of MSCs by reducing intracellular ROS levels (90). Ribose-5-phosphate, a key precursor for purine and pyrimidine nucleotide synthesis, promotes osteoblast proliferation and also induces the fusion of mononuclear precursors into osteoclasts. NADPH promotes type I collagen cross-linking to form a robust fibrous network and regulates intracellular redox balance in osteoclasts (83).

5. GLUTs in osteoblasts and osteoclasts

GLUTs comprise a large family of carrier proteins located on the cell membrane that facilitate glucose transport from regions of higher to lower concentration. GLUT1 appears to be abundant in early precursor cells, stable GLUT3 expression contributes to osteogenesis and GLUT4 expression is key to osteoblast proliferation and differentiation (91). GLUT1 is a potential target for osteoporosis treatment (92). GLUT1 increases glucose uptake to promote glycolysis and the TCA cycle during the osteogenic differentiation of MSCs (93,94). TGF-β-SMAD2/3 signaling modulates GLUT1 promoter activity and is involved in the balance between osteogenesis and adipogenesis (95). GLUT1 regulates sirtuin (SIRT)1/RUNX2 responses and activates AKT/glycogen synthase (GS) kinase-3β (GSK-3β) signaling to promote bone formation (96,97). Inhibition of GLUT1 can decrease RANKL expression and weaken bone resorption (98), whereas enhanced GLUT1 activity can increase the expression levels of RANK, CTSK and NFATc1 (99). GLUT1-mediated glycolysis contributes to HIF-1α-induced osteoclast differentiation (100). HIF-1α activates GLUT1 to promote MMP-9 and NF-κB expression (101). GLUT3 regulates the cell cycle

Table I. Anaerobic oxidation in osteogenesis and osteoclastogenesis.

Molecules	Mechanism	Effect in bone metabolism	(Refs.)
LDH	Increasing the expression levels of Sp7, IBSP and BGLAP	Promoting bone mineralization	65)
	Upregulation induced by mechanical loading	Enhancing bone strength	(66)
	Activating RANKL signaling	Promoting osteoclast differentiation	(67)
	Mediating the production of ROS	Inhibiting osteoclast differentiation	(68)
	Involved in mitochondrial redox homeostasis	Regulating osteoclast functions	(45)
Lactate (at low or physiological concentrations)	Endogenous activation of Wnt/β-catenin signaling	Increasing the expression levels of Sp7 and type I collagen	(69)
	Activating GPR81-JAK2/AKT-STAT3 signaling pathway	Promoting osteogenic differentiation	(70)
	Relieving oxidative stress damage by increasing the activity of SOD and CAT	Increasing osteogenesis and angiogenesis for vascularized bone formation	(71)
	Promoting M2 and inhibiting M1 polarization of macrophages	Enhancing the osteogenic effects of MSCs	(72)
	Used in the preparation of biomaterials	Promoting bone formation	(74)
	Lactate-enriched hydrogel scaffolds	Promoting bone regeneration and repairing bone tissue defects	(75)
	Inhibiting ROS production	Suppressing osteoclasts by reducing the expression levels of TRAP and CTSK	(76,77)

TRAP, tartrate-resistant acid phosphatase; JAK2, Janus kinase 2; CTSK, cathepsin K; Sp7, osterix; IBSP, integrin-binding sialoprotein; BGLAP, bone γ-carboxyglutamate protein; SOD, superoxide dismutase; CAT, catalase; ROS, reactive oxygen species; MSCs, mesenchymal stem cells; Sp7, osterix; LDH, lactate dehydrogenase; GPR81, G protein-coupled receptor 81; RANKL, receptor activator of NF-κB ligand.

and promotes osteoblast proliferation through the MAPK pathway (102). GLUT3 also improves redox balance and glycolysis during osteogenic differentiation (103). Together with GLUT1, GLUT3 induces glycolysis and the TCA cycle to supplement energy production and activates Wnt signaling to promote osteogenesis (104). GLUT3 is another transporter involved in HIF-1α-mediated osteoclastogenesis (101). GLUT4 is key to insulin-dependent glucose uptake and oxidation in osteoblasts (105). GLUT4 regulates osteocalcin (OCN) secretion during insulin induction and resistance (106). GLUT4-mediated energy metabolism promotes osteogenic mineralization and the expression levels of BMP2, p-SMAD1, RUNX2 and OCN (107). GLUT4 responsiveness to insulin sensitivity is beneficial in preventing bone loss (108). GLUT4 also helps reduce oxidative damage and inhibit bone resorption (109) (Table II).

6. Glucose metabolism in muscle-bone crosstalk

Muscle glycogen is the stored form of glucose in skeletal muscle. Adequate muscle glycogen reserves enable muscles to sustain longer and more forceful contractions, thereby providing stronger and more frequent mechanical stimuli to bone. Impaired muscle glycogen metabolism can reduce muscle mass and function, thereby increasing the risk of osteoporosis (110). Bone health largely depends on the mechanical stress generated by muscle contraction, which stimulates bone remodeling and strengthening in response to load (111). When muscle glycogen synthesis and storage are impaired, muscular endurance, strength and volume decline, leading to reduced mechanical stimulation of bone. In the absence of these key signals from muscle activity, the balance of bone remodeling is disrupted: Bone resorption accelerates, bone formation decreases, BMD declines and osteoporosis develops (112).

Endocrine signaling is a key bridge in the maintenance of muscle-bone crosstalk. Muscle contraction and glycogen metabolism stimulate the secretion of insulin-like growth factor-1 (IGF-1). IGF-1 deficiency is markedly associated with osteosarcopenia (113). IGF-1 not only promotes muscle protein synthesis but also enhances osteoblast activity and stimulates bone formation (114). IGF-1 activates the PI3K/AKT signaling pathway and induces GLUT4 translocation to promote glucose uptake in muscle tissue (115,116). IGF-1 also promotes muscle glycogen synthesis by inhibiting GSK-3 activity and enhancing GS activity (117). Inhibition of GSK-3 activity can enhance muscle force production and endurance, promote bone mineralization and increase BMD (118). Muscle-derived IGF-1 improves bone metabolism and increases OCN expression to promote osteogenesis (119). Increased IGF-1 levels in skeletal muscle also upregulate alkaline phosphatase, osterix and RUNX2 expression to promote osteogenic differentiation (120). Irisin secreted during muscle glycogen utilization can convert white adipocytes associated with fat storage into thermogenic brown adipocytes, while also directly stimulating osteoblast differentiation and increasing bone density (121). Irisin is a key myokine involved in regulating the RANKL/OPG system and pro-osteogenic cytokine activity (122,123). Irisin induces mitosis through 5'-AMP-activated protein kinase (AMPK)/unc-51-like autophagy activating kinase 1 (ULK1)

Table II. GLUTs in osteoblasts and osteoclasts.

GLUT	Mechanism	Effect in bone metabolism	(Refs.)
GLUT1	Increasing glucose uptake to promote glycolysis and TCA cycle	Promoting osteogenic differentiation of MSCs	(93,94)
	Modulated by TGF-β-SMAD2/3 signaling	Involved in the osteogenic and adipogenic balance	(95)
	Regulating SIRT1/RUNX2 responses and activating AKT/GSK-3β signaling	Promoting bone formation	(96,97)
	Decreasing the expression level of RANKL with GLUT1 inhibition	Weakening bone resorption	(98)
	Increasing the expression levels of RANK, CTSK and NFATc1	Promoting osteoclastogenesis	(99)
	GLUT1-mediated glycolysis involved in HIF-1α signaling	Inducing osteoclast differentiation	(100)
	Activated by HIF-1α	Promoting MMP-9 and NF-κB expression	(101)
GLUT3	Activating MAPK pathway	Promoting cell proliferation of osteoblasts	(102)
	Improving redox balance and glycolysis	Enhancing osteogenic differentiation	(103)
	Activating Wnt signaling	Promoting osteogenesis	(104)
	Involved in HIF-1α signaling	Inducing osteoclast differentiation	(101)
GLUT4	Key in insulin-dependent uptake and glucose oxidation of osteoblasts	Promoting osteogenesis	(105)
	Regulating osteocalcin secretion with insulin induction and resistance	Promoting osteogenic differentiation	(106)
	Promoting the expression levels ofBMP2, phosphor-SMAD1, RUNX2 and osteocalcin	Enhancing osteogenic differentiation	(107)
	Improving oxidative damage	Inhibiting bone resorption	(109)

GLUT, glucose transporter; NFATc1, nuclear factor of activated T-cells, cytoplasmic 1; CTSK, cathepsin K; RUNX2, runt-related transcription factor 2; BMP2, bone morphogenetic protein 2; HIF-1α, hypoxia-inducible factor-1α; RANK, receptor activator of NF-κB; RANKL, RANK ligand; SIRT1, sirtuin 1; TCA cycle, citric acid cycle; MSCs, mesenchymal stem cells; GSK-3β, glycogen synthase kinase-3β.

signaling and mitochondrial autophagy, thereby promoting osteoblast proliferation and reducing oxidative damage (124). Irisin also activates β-arrestin-2-dependent p38MAPK and JNK signaling to promote osteogenic differentiation and mineralization (125). β-aminoisobutyric acid (BAIBA) is another exercise-induced myokine that promotes osteoblast differentiation and inhibits osteoclastogenesis. BAIBA activates Mas-associated GPR type D signaling to prevent ROS-induced mitochondrial damage in osteoblasts (126). BAIBA also increases fibroblast growth factor 23 levels in bone tissue to promote osteogenic differentiation (127). Furthermore, BAIBA inhibits PI3K/AKT/NF-κB signaling and activates the nuclear factor erythroid 2-related factor 2-mediated antioxidant system to suppress osteoclastogenesis (128) (Fig. 2).

7. Glucose metabolism in postmenopausal osteoporosis

Postmenopausal osteoporosis is a metabolic bone disease characterized by rapid bone loss and deterioration of bone microarchitecture due to the marked decline in estrogen levels after menopause. Estrogen notably enhances glucose uptake and utilization in osteoblasts through both direct and indirect mechanisms, directing these cells toward efficient OXPHOS to meet energy demands while promoting differentiation and bone-forming functions (129). Estrogen deficiency triggers glucose metabolic reprogramming in osteoblasts, shifting cellular metabolism from oxidative metabolism toward glycolysis (130). This disruption of energy metabolism is a key factor that impairs osteoblast function and contributes to insufficient bone formation.

Estrogen enhances basal glucose uptake by increasing the transcription and protein expression level of GLUT1 through its receptor (131). Estrogen also increases GLUT4 expression and translocation by activating PI3K/AKT phosphorylation and increasing G protein-coupled estrogen receptor (ER) expression (132). In bilaterally ovariectomized (OVX) mice, reduced GLUT expression weakens osteoblast differentiation (133). Estrogen may increase adiponectin secretion during bone metabolism and upregulate peroxisome proliferator-activated receptor-γ (PPARγ) coactivator 1-α (PGC-1α) expression to promote mitochondrial respiration during osteogenic differentiation (134). Downregulation of PGC-1α and SIRT3 drives OVX-MSC senescence through suppression of ERα-mediated mitochondrial biogenesis (135). Enrichment analysis of clinical serum samples suggested that OXPHOS is closely associated with the development of postmenopausal osteoporosis (136). Estrogen deficiency markedly inhibits OXPHOS by reducing the synthesis of ATP-producing intermediates in

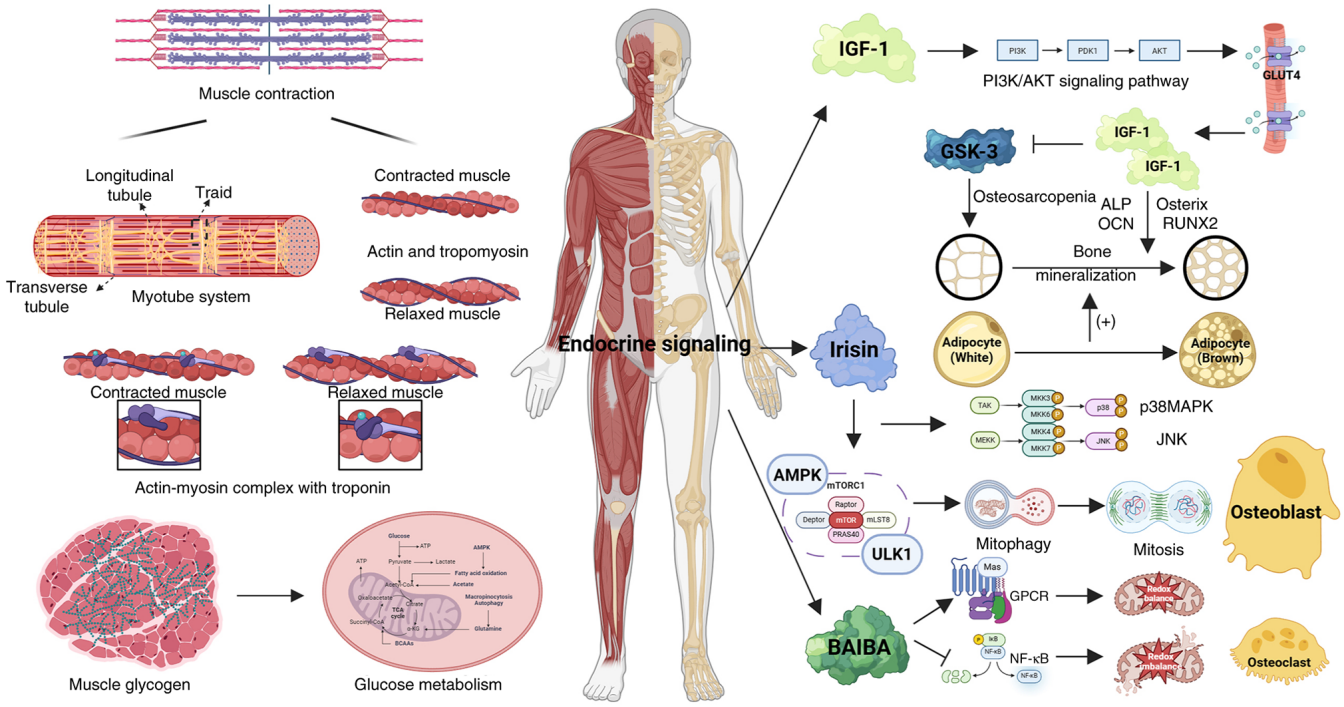

Figure 2. Glucose metabolism in muscle-bone interaction. Endocrine signaling is a key bridge in the maintenance of muscle-bone crosstalk. IGF-1 activates the PI3K/AKT signaling pathway and induces GLUT4 translocation to promote glucose uptake in muscle tissue. IGF-1 also promotes muscle glycogen synthesis by inhibiting GSK-3 activity and enhancing GS activity. Irisin induces mitosis through AMPK/ULK1 signaling and mitochondrial autophagy and activates β-arrestin-2-dependent p38MAPK and JNK signaling to promote osteogenic differentiation and mineralization. BAIBA activates Mas-related GPCR type D signaling to prevent ROS-induced mitochondrial damage in osteoblasts and inhibits PI3K/AKT/NF-κB signaling. Black arrows indicate a progressive relationship. (+) indicates a positive effect. BAIBA, β-aminoisobutyric acid; IGF-1, insulin-like growth factor-1; AMPK, 5'-AMP-activated protein kinase; ULK1, unc-51-like autophagy activating kinase; NRF2, nuclear factor erythroid 2-related factor 2; GLUT, glucose transporter; ROS, reactive oxygen species; GS, glycogen synthase; GSK-3, GS kinase-3; GPCR, G protein-coupled receptor.

osteoblasts (137). Furthermore, estrogen regulates mitochondrial redox balance and mitophagy to maintain mitochondrial respiratory efficiency (135). Estrogen deficiency weakens mitochondria-lysosome interactions, reduces mitochondrial metabolism and thereby impairs bone healing (138). Impaired autophagic flux also induces mitochondrial redox imbalance and suppresses osteoblast activity and mineralization (139).

The differentiation of osteoclasts in women is specifically dependent on mitochondrial glucose oxidation (56). Estrogen can inhibit RANKL-induced activation of complex I activity and OXPHOS for mitochondrial ATP production and can induce mitochondrial apoptosis in osteoclasts (140). Estrogen inhibits evolutionarily conserved signaling intermediate in Toll pathway binding to TNF receptor-associated factor 6, thereby suppressing the initiation of mitochondrial complex I activity (141). Estrogen deficiency activates the AMPK-PGC-1β pathway to promote mitochondrial ATP production during osteoclast differentiation (142) (Table III). In women, estrogen confers resistance to bone loss by suppressing mitochondrial energy metabolism and NAD^+ levels through the CREB/malate dehydrogenase 2 axis in osteoclasts (143) (Fig. 3).

8. Glucose metabolism in diabetic osteoporosis

Diabetic osteoporosis is a complication of type 2 diabetes mellitus characterized by decreased bone density and increased bone fragility resulting from long-term hyperglycemia and insulin abnormalities (144,145). Prolonged hyperglycemia leads to excessive production of advanced glycation end-products (AGEs), which damage bone collagen and deteriorate bone quality (146). AGEs induce osteoblast apoptosis by enhancing oxidative damage and inhibiting mitochondrial ATP production (147). AGE-specific receptors mediate ROS accumulation, triggering oxidative stress and activating the NF-κB-dependent inflammatory pathway, thereby exacerbating the cellular energy burden in osteoblasts. ROS-induced destruction of the mitochondrial inner membrane reduces membrane potential and markedly decreases ATP synthesis efficiency (148). AGEs also interfere with energy sensors in osteoblasts by acting on the AMPK and mTOR signaling pathways (149,150). Furthermore, a single study has indicated that AGE accumulation can increase osteoclast activity, induce bone loss and contribute to osteoporosis (151).

Hyperglycemia provides abundant glucose substrate for glycolysis in osteoclasts. Insulin resistance or deficiency impairs the capacity of osteoblasts to use glucose efficiently for energy production and compromises osteoblast function (152). Under physiological conditions, insulin promotes glucose uptake by facilitating GLUT4 translocation to the cell membrane through activation of the insulin receptor substrate (IRS)/PI3K/AKT signaling pathway. Reduced insulin sensitivity markedly suppresses GLUT4-mediated glucose uptake and disrupts glucose metabolism in osteoblasts (105). Insulin deficiency reduces glucose uptake and suppresses glycolysis, resulting in decreased ATP production in osteoblasts (153). This energy deficit is insufficient to support the notable

Table III. Glucose metabolism defects in osteoporosis.

Cells	Glucose metabolism	Postmenopausal osteoporosis	Diabetic osteoporosis	Obesity-associated osteoporosis
OB	Glucose metabolism pathway	Shifts from oxidative metabolism to glycolysis	Insulin deficiency inhibits glycolysis, leading to decreased ATP production	Inflammatory factors inhibit glycolysis to weaken osteogenesis
	Glucose transport	Decreased GLUT expression weakens the differentiation	Reduced insulin sensitivity inhibits GLUT4-mediated glucose uptake	IL-1β inhibitsGLUT4-mediated glucose uptake by promoting IRS phosphorylation
	OXPHOS	Estrogen deficiency inhibits OXPHOS by reducing the synthesis of ATP-producing intermediates	Insulin resistance inhibits FOXO/β-catenin signaling to induce OXPHOS disturbance	Adiponectin enhances OXPHOS to meet the energy demands for differentiation and mineralization
	Signaling pathways	Estrogen deficiency weakens the interaction of mitochondria and lysosome to reduce mitochondrial metabolism	Inactivation of the IRS/PI3K/AKT suppresses the expression levels of BGLAP and OCN	IL-6 activates the JAK/STAT and MAPK pathways to trigger insulin resistance
OC	Glucose metabolism pathway	Differentiation of osteoclasts is dependent on the mitochondrial oxidation of glucose	Hyperglycemia provides notable supply of glucose substrate for glycolysis	Inflammatory factors promote glycolysis to induce macrophage recruitment
	OXPHOS	RANKL activates complex I activity and OXPHOS for mitochondrial ATP production	Insulin resistance enhances NF-κB signaling pathway to induce OXPHOS disturbance	-
	Signaling pathways	Activating AMPK-PGC-1β pathway to promote mitochondrial ATP production for osteoclast differentiation	Accumulation of AGEs increases the activity of osteoclasts to induce bone loss	-

OB, osteoblast; OC, osteoclast; JAK, Janus kinase; OCN, osteocalcin; GLUT, glucose transporter; OXPHOS, oxidative phosphorylation; AMPK, 5'-AMP-activated protein kinase; AGEs, advanced glycation end-products; IRS, insulin receptor substrate; ILs, interleukins; BGLAP, bone γ-carboxyglutamate protein; OCN, osteocalcin; RANKL, receptor activator of NF-κB ligand; PGC-1β, peroxisome proliferator-activated receptor γ coactivator 1-β.

energy demands required for abundant bone matrix protein synthesis (154). Insulin resistance inhibits FOXO/β-catenin signaling and enhances the NF-κB signaling pathway, thereby inducing OXPHOS disturbance in bone tissue (155). mTOR signaling also serves a key role in bone metabolism regulated by insulin sensitivity-mediated glucose homeostasis (156). Hyperglycemia hyperactivates an mTOR complex-dependent negative feedback loop, which in turn induces insulin resistance in osteoblasts. Subsequent inactivation of the IRS/PI3K/AKT signaling pathway suppresses BGLAP and OCN expression and markedly reduces BMD (157) (Fig. 3) (Table III).

9. Glucose metabolism in obesity-associated osteoporosis

Obesity is a major risk factor for osteoporosis (11). Excess adipose tissue releases large quantities of pro-inflammatory cytokines, such as TNF-α and interleukins (ILs). These inflammatory factors promote osteoclast activation and accelerate bone resorption, while simultaneously inhibiting osteoblast differentiation and slowing bone formation (158). Abnormal secretion of adipokines, including leptin and adiponectin, is also associated with bone loss in individuals with obesity (159).

In individuals with obesity, systemic insulin resistance desensitizes the IRS/PI3K/AKT signaling pathway in osteoblasts. This impairs glucose uptake and utilization, thereby inducing a state of cellular starvation or energy deficiency. Therefore, osteoblast proliferation, differentiation and collagen synthesis are compromised (160). Chronic inflammation is a pathological alteration involved in obesity-mediated metabolic disorder in osteoblasts (161). The pro-inflammatory cytokines TNF-α and IL-6 activate inflammatory signaling pathways such as NF-κB and JNK, leading to IRS degradation and

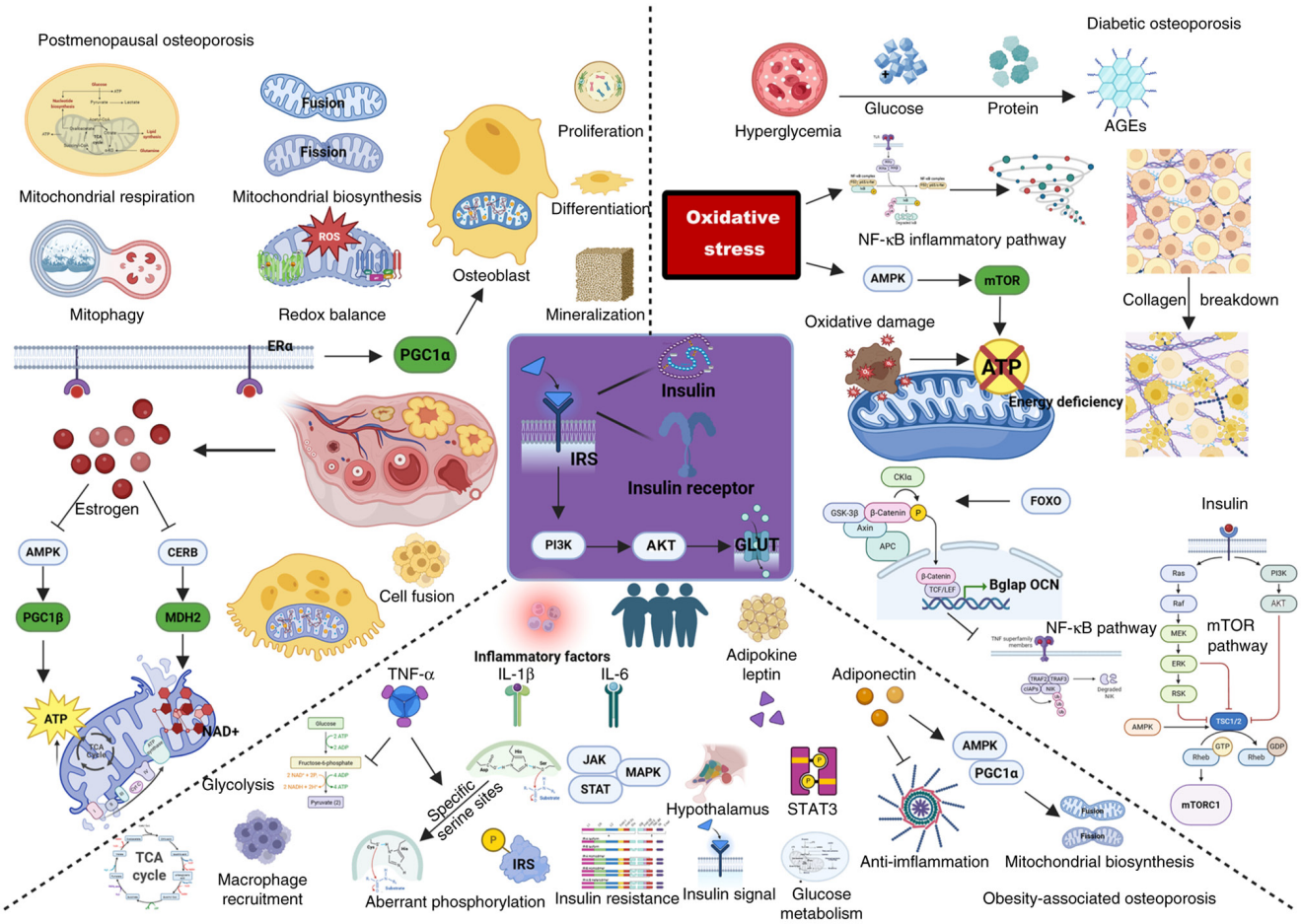

Figure 3. Glucose metabolism in the high-risk populations for osteoporosis. Postmenopausal women, patients with type 2 diabetes mellitus and individuals with obesity are the high-risk populations for osteoporosis. The IRS/PI3K/AKT signaling pathway is a common pathogenesis of osteoporosis, which acts on the GLUTs to regulate glucose transport. Estrogen receptor regulates mitochondrial function through PGC-1α, including biogenesis, respiration, mitophagy and redox regulation, thereby affecting the proliferation, differentiation and mineralization of osteoblasts. AGE-specific receptors mediate ROS accumulation, triggering oxidative stress and activating the NF-κB-dependent inflammatory pathway, thereby exacerbating the cellular energy burden in osteoblasts. AGEs also interfere with energy sensing in osteoblasts by acting on the AMPK and mTOR signaling pathways. Chronic inflammation is a pathological alteration involved in obesity-mediated metabolic disorder in osteoblasts. Pro-inflammatory cytokines activate inflammatory signaling pathways such as NF-κB and JNK, leading to IRS degradation and blockade of insulin signal transduction. Black arrows indicate a progressive relationship. The black and red lines indicate negative effects. GLUTs, glucose transporters; PGC, peroxisome proliferator-activated receptor-γ coactivator; IRS, insulin receptor substrate; AGEs, advanced glycation end-products; AMPK, 5'-AMP-activated protein kinase; ROS, reactive oxygen species; p, phosphorylated; JAK, Janus kinase; BGLAP, bone γ-carboxyglutamate protein; OCN, osteocalcin.

blockade of insulin signal transduction. This impairs glucose transporter translocation to the cell membrane and thus, prevents efficient cellular glucose uptake (162,163). TNF-α acts on specific serine sites of IRS-1 and induces aberrant phosphorylation, thereby interrupting insulin signaling (164). Excessive TNF-α production also suppresses bone formation by inducing the loss of mitochondrial membrane potential and ATP (165). TNF-α further inhibits osteoblast glycolysis, weakens osteogenesis and promotes macrophage recruitment for osteoclast differentiation (166). IL-1β inhibits GLUT4-mediated glucose uptake by promoting IRS phosphorylation via activation of the IKKβ pathway (167). Binding of IL-6 to its receptor activates intracellular JAK/STAT and MAPK pathways, triggering insulin resistance (168,169).

Leptin is an adipose tissue-derived hormone that regulates behavior and metabolism. Leptin exerts dual effects on osteoblast glucose metabolism and function, comprising central inhibitory and peripheral stimulatory effects. Leptin inhibits insulin signaling in osteoblasts by activating the hypothalamic sympathetic nervous system to release norepinephrine, which binds to the β2-adrenergic receptor (170). The β2-adrenergic receptor is negatively associated with subchondral bone remodeling (171). By contrast, leptin directly binds to leptin receptors on osteoblasts and activates the STAT3 signaling pathway to enhance glucose metabolism and promote osteogenic gene expression (172). Adiponectin is an insulin-sensitizing hormone that improves insulin resistance. By binding to surface receptors and activating AMPK signaling, adiponectin enhances the sensitivity of the IRS/PI3K/AKT signaling pathway in osteoblasts (173). Adiponectin promotes mitochondrial biogenesis by activating AMPK and PGC-1α, thereby enhancing OXPHOS to efficiently generate ATP and meet the energy demands of osteoblast differentiation and mineralization (174). Adiponectin also has potent anti-inflammatory properties, suppressing the release of the aforementioned inflammatory cytokines and thereby alleviating their detrimental effects on glucose metabolism in osteoblasts (175) (Fig. 3).

10. Clinical evidence of therapeutic targets in high-risk populations for osteoporosis

Osteoporosis-associated therapeutic targets at the interface of skeletal and glucose metabolism can be conceptualized as a three-tier framework. The first tier comprises clinically validated bone-remodeling targets, including the osteoclast mevalonate pathway/farnesyl pyrophosphate synthase axis, RANKL, parathyroid hormone 1 receptor and the sclerostin-Wnt/β-catenin pathway (176). The second tier consists of glucose-lowering or weight-loss-associated metabolic targets that indirectly modify skeletal risk, including PPARγ and glucagon-like peptide-1 receptor (GLP-1R). PPARγ represents the most notably established adverse skeletal target, as thiazolidinedione treatment has been associated with increased fracture risk, particularly in women, and pioglitazone increased fracture risk in randomized clinical trial safety analyses (177-179). GLP-1R agonists should be interpreted in the context of weight reduction, nutrition and physical activity; a randomized clinical trial demonstrated that liraglutide combined with exercise achieved weight loss while preserving bone health, whereas liraglutide alone further reduced BMD at the hip and lumbar spine compared with exercise alone despite similar weight loss (180). The third tier includes candidate bone-glucose endocrine and metabolic targets, such as insulin/IGF-1-IRS-PI3K-AKT signaling, AGE/receptor for AGE and OCN/GPR class C group 6 member A. IGF-1 has been supported by Mendelian randomization as a potential protective factor for BMD and fracture risk, whereas OCN remains an endocrine candidate linking bone turnover with glucose metabolism, although further evidence from human studies is warranted as the findings are largely associative (181-183). Obesity-associated osteoporosis further illustrates the limitations of BMD-centered assessment: Obesity is not uniformly protective against fracture in postmenopausal women, with site-specific fracture patterns reported in cohort studies and meta-analyses (184,185). Therefore, in postmenopausal, type 2 diabetic and obesity-associated osteoporosis, treatment should be based on standard anti-osteoporotic therapies when fracture risk is high, while simultaneously incorporating glycemic control, avoidance of bone-harmful antidiabetic drugs, individualized weight management, nutritional optimization, exercise-based muscle-bone preservation and fall prevention (12).

11. Discussion

Osteoporosis is a pathological process driven by an imbalance between bone formation and resorption. The exact pathogenesis of osteoporosis remains incompletely understood. Current pharmacological treatments, such as teriparatide, romosozumab, bisphosphonates and denosumab, primarily focus on directly promoting bone formation or inhibiting bone resorption; however, therapeutic efficacy remains limited. Furthermore, osteoporosis has a multifactorial etiology, including estrogen deficiency, hyperglycemia and obesity, which complicates the development of precise therapeutic strategies. Glucose metabolism is the enzymatically regulated process by which sugar substrates are broken down to supply energy, synthesized for storage and interconverted in living organisms. The physiological functions of glucose metabolism include generating energy (ATP) and carbon skeletons to sustain life activities. Multiple studies have demonstrated that disordered glucose metabolism is a shared pathological alteration underlying various forms of osteoporosis (186-188).

The present review provided a detailed overview of GLUT-mediated cellular glucose uptake, the major pathways of glucose oxidation and the key enzymes involved in glucose metabolism. Each key step in glucose metabolism contributes to the regulation of bone tissue homeostasis. GLUTs facilitate glucose diffusion down its concentration gradient from the extracellular to the intracellular compartment. Since glucose molecules are hydrophilic, GLUTs provide a key route for cellular glucose entry. GLUT1 and GLUT3 primarily support the initial stage of osteogenic differentiation of MSCs by mediating glycolysis, whereas GLUT4 directly promotes osteoblast maturation by enhancing osteogenic gene expression through OXPHOS (91). Systematic modulation of GLUT isoform ratios may facilitate efficient osteogenesis. Aerobic glucose oxidation is the most efficient energy-producing pathway in glucose metabolism and represents the primary mechanism by which human cells generate energy under sufficient oxygen supply. Osteoblasts synthesize and secrete large amounts of type I collagen and non-collagenous proteins, including OCN and osteopontin. The synthesis, folding, modification and transport of these proteins are energy-intensive processes. Osteoblasts also require energy to establish and maintain their unique cellular architecture by initiating and controlling hydroxyapatite deposition during bone mineralization. Aerobic oxidation also functions as a signaling mechanism that prevents excessive AMPK activation and modulates histone acetylation, thereby promoting osteogenic differentiation (189,190). Anaerobic oxidation is the process by which cells incompletely break down glucose and produce a small amount of energy under oxygen-deficient conditions. Osteoclast energy metabolism is predominantly biased toward anaerobic glycolysis. Simultaneously, osteoclasts secrete proteases such as CTSK to degrade collagen (191). The resorption compartment created by osteoclasts is an acidic and hypoxic microenvironment. Aerobic oxidation in mitochondria is inefficient under these conditions, whereas anaerobic glycolysis can proceed. The glycolytic enzyme system is located in the cytoplasm, enabling direct and efficient ATP supply to proton pumps on the cell membrane. Furthermore, as a key bypass pathway of glucose metabolism, the PPP provides reducing power for biosynthesis and is associated with multiple metabolic pathways. Ribose-5-phosphate and NADPH are the primary metabolic products of the PPP.

At present, the clinical evidence regarding insulin sensitizers in individuals with osteoporosis remains inconsistent. Metformin, one of the most extensively used insulin-sensitizing agents, may exert potential skeletal benefits by modulating energy metabolism, inflammatory responses and osteogenic signaling pathways. However, current systematic evidence indicates that metformin does not markedly improve BMD at the lumbar spine, femoral neck or total hip; its effects appear to be more evident for selected bone turnover markers (192-194). By contrast, although thiazolidinediones enhance peripheral insulin sensitivity, activation of PPARγ may promote adipogenic differentiation of bone marrow

MSCs while suppressing osteoblast differentiation and bone formation. Clinical randomized studies have reported that rosiglitazone can reduce BMD and increase bone turnover in postmenopausal women (195,196). Some clinical studies have further indicated that rosiglitazone or pioglitazone use is associated with an increased risk of fracture, particularly among women, postmenopausal individuals and patients with established osteoporosis or a high baseline fracture risk (177,179). Therefore, the IRS/PI3K/AKT signaling pathway may be notably viewed as a mechanistic framework associating dysregulated glucose metabolism with impaired skeletal homeostasis, while also providing a rationale for the development of more bone-targeted therapeutic strategies in the future.

The present review supports a shift from viewing osteoporosis solely as an imbalance between osteoblasts and osteoclasts toward conceptualizing it as a systemic metabolic bone disorder. Clinically, glucose metabolism may provide a useful framework for risk stratification and individualized management. In postmenopausal women, assessment of metabolic status may help identify patients in whom estrogen deficiency is accompanied by mitochondrial dysfunction, insulin resistance or sarcopenic decline (184). In patients with type 2 diabetes mellitus, fracture assessment should not rely exclusively on BMD, because hyperglycemia, AGE accumulation, impaired bone material properties, neuropathy and fall risk may increase skeletal fragility despite apparently preserved bone mass. In individuals with obesity, clinicians should distinguish metabolically healthy obesity from inflammatory or sarcopenic obesity, because these subtypes may differ markedly in bone quality and fracture risk. Therapeutically, targeting glucose metabolism does not imply replacing established antiresorptive or osteoanabolic therapy; by contrast, it provides a complementary strategy that may include improving insulin sensitivity, preserving mitochondrial function, reducing oxidative and glycation stress, maintaining muscle-bone mechanical coupling and optimizing exercise and nutritional interventions.

However, several limitations should be acknowledged when interpreting the current evidence. Majority of the mechanistic evidence associating glucose metabolism with bone remodeling derives from *in vitro* cell systems or animal models (197,198), whereas direct evidence from human bone tissue remains limited (199,200). Several metabolic mediators described in the present review, including lactate, ROS, NADPH, insulin signaling and adipokines, have dual or context-dependent effects. Lastly, although glucose metabolism is notably associated with osteoporosis-related phenotypes, clinical trial evidence remains insufficient to demonstrate that direct correction of bone-cell glucose metabolism alone can prevent fractures or reverse established osteoporosis. Therefore, the current evidence supports glucose metabolism as a central pathogenic and therapeutic framework; however, not yet as a fully validated therapeutic target. Future studies should progress from association-based descriptions toward causal and translational validation (201). At the clinical level, longitudinal cohorts should integrate hemoglobin A1c variability, fasting insulin, insulin-resistance surrogates, AGEs or pentosidine, circulating lactate, lipid-inflammatory markers, irisin, muscle mass and function, dual-energy X-ray absorptiometry, trabecular bone score, high resolution-peripheral quantitative CT and fracture outcomes. Such designs would potentially clarify whether metabolic biomarkers predict bone fragility beyond traditional BMD in the future.

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Authors' contributions

SP curated the data, designed literature search strategies (databases and key words), established inclusion/exclusion criteria, defined quality assessment methods, conducted systematic literature searches, screened and selected relevant sources, extracted key data or viewpoints, compiled evidence tables, and wrote the original draft of the manuscript. ZY curated the data, conducted systematic literature searches, screened and selected relevant sources, extracted key data or viewpoints, compiled evidence tables, and wrote the original draft of the manuscript. JG designed literature search strategies (databases and key words), established inclusion/exclusion criteria, defined quality assessment methods, conducted systematic literature searches, screened and selected relevant sources, extracted key data or viewpoints, compiled evidence tables, and wrote the original draft of the manuscript. CZ curated the data, designed literature search strategies (databases and key words), established inclusion/exclusion criteria, defined quality assessment methods, validated the data, and reviewed and edited the manuscript. KY curated the data, conducted systematic literature searches, screened and selected relevant sources, extracted key data or viewpoints, compiled evidence tables, validated the data, and reviewed and edited the manuscript. LT acquired funding for the present review, participated in project administration, obtained resources, and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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